REMARKS

Reconsideration of the application is respectfully requested. Claims 23, 29, and 35 have been canceled without prejudice or disclaimer. No new matter has been added. Claims 21, 25, 27, 31, 33, and 37 are pending and at issue.

Indefiniteness Rejection

Claims 23, 29, and 35 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

Without conceding the correctness of this rejection, claims 23, 29, and 35 have been canceled without prejudice or disclaimer. Therefore, this rejection should be withdrawn.

Obviousness Rejection

Claims 21, 23, 25, 27, 29, 31, 33, 35, and 37 have been rejected under 35 U.S.C. § 103(a) as obvious over Patris et al. (*Int. Clin. Psychopharm.* 11:129-136 (1996)) in view of Boegesoe et al. (U.S. Patent No. 4,943,590), and Bilski et al. (U.S. Patent No. 4,764,361). The Examiner contends that Patris discloses administration of citalopram to treat patients with major depression, with efficacy measured using MADRS scores and the CGI severity and improvement scale. The Examiner concedes that Patris does not teach escitalopram. The Examiner relies on Boegesoe as disclosing that the entire 5-HT uptake inhibition activity resides in escitalopram. The Examiner states that Bilski generally teaches the oxalate and crystalline salts of the (S) form of a racemic mixture, but does not specifically refer to escitalopram. The Examiner concludes that in view of these references it would have been obvious to one of ordinary skill in the art to use the crystalline and oxalate salts of escitalopram in a method of treating severe depression.

Claims 23, 29, and 35 have been canceled without prejudice rendering the rejection of these claims moot.

As to the remaining claims, applicants traverse the rejection and respectfully request reconsideration.

Even assuming, *arguendo*, that the cited references superficially support an obviousness rejection, evidence of unexpected results can rebut a *prima facie* case of obviousness. *See* MPEP §716.02(a). In the response filed November 20, 2006, applicants argued that the administration of escitalopram to treat severe depression in a patient having a MADRS score of at least 29 would not have been obvious because the administration of escitalopram is unexpectedly therapeutically superior compared to the administration of placebo or citalopram. This arguments was supported by references to data in the specification. However, in the March 27, 2007 Office Action, the Examiner states that these arguments "are not drawn to *factual support* in relevance to overcoming said obviousness rejections" (*see* Office Action, page 2) (emphasis added).

In treating depression, one way to evaluate a therapy is to determine a patient's MADRS score and monitor any changes in the score during treatment. The objective of treatment is to lower the MADRS score, since higher MADRS scores represent depression of increasing severity, and lower scores represent improvement. The Clinical Study results disclosed in the specification demonstrated that escitalopram lowered patients' MADRS scores surprising well, especially compared to treatment with citalopram. Additionally, applicants indicated that a full description of the study protocol and results that are disclosed in the specification could be found in Lepola, et al., *Clin. Psychopharm.*, 18(4):211-217 (2003), a complete copy of which was attached to the November 20th response.

In the study, subjects were treated with 20 mg/day citalopram, 10 mg/day escitalopram, or placebo for the first four weeks of the study, with the option of doubling the dosages at week 4 or week 6 (Lepola at p. 213). After eight weeks of treatment, the mean change in MADRS total score for escitalopram was 2.9 points better than placebo (the mean change in MADRS total score was 15.0 points for the escitalopram group, compared to only 12.1 points for the placebo group) (Lepola at p. 213, left column, and Fig 1). This was surprising because the effect was not the same, as if equal doses of escitalopram were administered in a pure vs. a

racemate formulation (where the R-enantiomer was thought to be essentially inert). Additionally, the results for escitalopram vs. placebo were statistically significant ($P = 0.002$). Citalopram, on the other hand, did not yield a statistically significant improvement (Lepola at p. 213, left column and Fig 1).

Thus, the clinical study and underlying the arguments presented in the November 20th response, and described at pages 6-7 of the specification, disclose factual data including: i) the study type (4 week randomized trial); ii) the breakdown of the study participants (number, sex, race, age, mean baseline MADRS total score); and iii) the statistical results (adjusted mean MADRS score, adjusted mean change in MADRS total score). These factual data are relevant to the non-obviousness of the claimed invention because they directly support the unexpected superiority of escitalopram compared to administration of citalopram for the treatment of patients suffering from severe depression and having a MADRS score of at least 29.

These results of superiority in the treatment of severe depression were unexpected. In particular, applicants pointed out that:

> the superior efficacy of escitalopram would not have been expected by one of ordinary skill in the art in view of the cited references. Citalopram is a racemate, containing both R-citalopram and escitalopram. Boegesoe teaches that almost the entire 5-HT uptake inhibition activity of citalopram resides in the S-enantiomer (col. 2, lines 40-42). Based on Boegesoe, escitalopram would be expected, at best, to be twice as potent as citalopram (*see* specification, p. 2, lines 13-15). Escitalopram, however, was found to be more than twice as potent in the study. In the first four weeks of the study, one group received 20 mg citalopram (which contains about 10 mg escitalopram) and another group received 10 mg escitalopram. A person of ordinary skill in the art would have expected similar therapeutic efficacy to be observed in both treatment groups during this four week period because each group received approximately 10 mg of escitalopram. In contrast, the experimental results revealed that treatment with escitalopram was therapeutically superior to citalopram ($p<0.01$) (*see* Fig. 1 of Lepola).

(Page 6-7 of the November 20th response).[1]

[1] Citalopram is a racemate, containing equal parts of the R and S enantiomers. Escitalopram is the S-enantiomer. Thus, if all of the therapeutic effect of citalopram resides in escitalopram, the therapeutic effect of one dose of escitalopram should be the same as two doses of citalopram. However, the data show, surprisingly, that in

These results are therefore both *significant* and *unexpected*. A person of ordinary skill in the art would not have expected that administration of escitalopram alone would provide a therapeutic efficacy that is so superior to that achieved when both S and R enantiomers were administered together (i.e., superior to the administration of citalopram). The inventors surprisingly discovered that the R-enantiomer in citalopram has a *negative* effect on escitalopram resulting in citalopram's inferior efficacy in severely depressed patients (*see* specification, p. 2, lines 13-14). In other words, administration of citalopram surprisingly did not lower patients' MADRS scores as much as administration of escitalopram. None of the cited references teach or suggest the detrimental influence of the R-enantiomer, or conversely that administration of escitalopram alone would provide the demonstrated superior therapeutic effect over racemic citalopram. *See* page 7 of the November 20th response.

The Examiner did not comment on, or even acknowledge, these factual data that support the unexpected superiority of treating patients suffering from severe depression and having a MADRS score of at least 29. Respectfully, this evidence should be considered and the rejection withdrawn.

Several published studies further support the surprising effect of treating severely depressed patients with escitalopram, when compared to citalopram. Pooled data have shown clear evidence of the superiority of escitalopram compared to citalopram in patients having a MADRS score representative of severe depression. *See* Figures 2 and 4 and page 32 (left column, third paragraph) of Gorman et al., *MedWorks Media*, April 2002) (Attachment A). The patients in these studies were treated with 10-20 mg/day escitalopram or 20-40 mg/day citalopram. In the patients having a MADRS score of at least 30:

> the effect of escitalopram was rapid and sustained (Figure 4). In both LOCF and OC analyses, escitalopram was found to be superior to citalopram in reducing symptomatology [that determines the MADRS score] among the severely depressed at weeks 1, 6, and 8.

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comparisons of X mg of escitalopram (e.g. 10 mg) vs. 2X mg of citalopram (e.g. 20 mg), the therapeutic effect was not the same. Escitalopram was surprisingly more effective alone than when administered with the R-entantiomer as part of the racemate.

For all variables, statistical analyses were conducted using both LOCF (last-observation carried forward) and OC (observed cases) (*Id.*). The authors, while noting that additional placebo-controlled comparative data in severely depressed patients would be helpful, concluded:

> For patients with baseline MADRS scores of at least 30 (indicative of severe depression), escitalopram treatment led to statistically significantly greater improvement at end point (LOCF values) than citalopram treatment. This could represent a distinct advantage for using escitalopram in these patients; however, there has been a paucity of placebo-controlled comparative data thus for SSRI antidepressants in severely depressed patients.

(page 44, left column, second full paragraph).[2]

It has also been found that the surprising results of the claimed invention are more profound as a patient's baseline MADRS score increases, i.e., as the severity of depression is increased. *See, e.g.,* Lam, et al. *Pharmacopsychiatry*, 39:180-184 (2006) (Attachment B) and Lepola et al., *Int. Clin. Psychopharmacol.*; 19:149-155 (2004) (Attachment C). Lam demonstrated that treatment with escitalopram resulted in clinical superiority when compared to citalopram in patients having a higher baseline MADRS score (*see* Lam, Figures 1-3). Lam concludes that "[t]hese extended trend analyses from the pooled placebo-controlled studies of escitalopram vs. citalopram indicates that the superiority of escitalopram becomes more apparent as the baseline severity increases" (*see* Lam, page 182, col. 2), such as for example, as in patients with MADRS scores that increase beyond 29 as claimed.

Similarly, Lepola found that

> the pooled results in the severely ill patients (baseline MADRS $\geq$ 30) revealed a significantly greater decrease in MADRS total score in the escitalopram group than the citalopram group (estimated difference 2.92; P = 0.029, OC; estimated difference 2.67; P =0.043, LOCF) (Fig. 6). The difference between escitalopram and

[2] As always, additional studies confirming these results would be helpful, and as understood by applicants, the "paucity" of data refers to comparisons among all SSRI antidepressant therapies & not just escitalopram vs. citalopram. The data for this particular comparison, as outlined in this Response, consistently show that escitalopram is superior to citalopram when they were expected to be equivalent.

> citalopram in the severely ill was so great that it was also statistically significant for the fixed dose study alone (estimated difference 4.24, 20 mg/day escitalopram versus 40 mg/day citalopram; $P = 0.045$, OC; $P = 0.125$, LOCF).

(paragraph spanning pages 152-153).

Lepola concludes that this analysis of "severely ill patients (baseline MADRS $\geq$ 30) demonstrated that the efficacy of escitalopram was superior to citalopram (OC and LOCF), and suggests that there could be a distinct clinical advantage in using escitalopram in this patient population" (page 154, right col., second full paragraph).

Additionally, Moore et al., *Int. Clin. Psychopharm.*, 20(3):131-137 (2005) (Attachment D), reported a study comparing treatment of patients having a MADRS score of at least 30 with 20 mg escitalopram or 40 mg citalopram. "Patients were four-fold more likely to withdraw because of a lack of efficacy in the citalopram-treated group than in the escitalopram-treated group (2.8 versus 0.7%, respectively, $P = 0.19$), and more than two-fold more likely to withdraw due to adverse events (6.3 versus 2.9%, respectively; $P = 0.17$) (Table 1)" (page 133, left col., penultimate paragraph). The mean reduction in MADRS score was significantly greater in patients treated with escitalopram than in patients treated with citalopram (page 133, right col., to page 134, left col.). Furthermore, there were "significantly more responders (50% decrease from initial MADRS score) at end-of-study in the escitalopram group than in the citalopram group (76.1 versus 61.3%, $P = 0.008$) (Fig. 2)." The authors concluded that

> [t]he consistent pattern of a difference in antidepressant effect between citalopram and escitalopram across several clinically relevant measures demonstrates a true therapeutic effect attributable to escitalopram.
>
> The greater efficacy of escitalopram compared to citalopram found in the present study is in accordance with the results from numerous animal models at the neurochemical, functional and behavioral levels. ... Figure 3 summarizes the results from these pre-clinical studies. All of these studies confirm that the R-citalopram isomer inhibits the effect of escitalopram when both are given at equivalent doses. This inhibition increases with increasing

> doses of R-citalopram. The R-enantiomer significantly inhibited the S-enantiomer effect in a dose-dependent manner, such that the effect of escitalopram is different in the presence or absence of R-citalopram.

(pages 135-136).

The foregoing studies further support that escitalopram (the S-enantiomer) has unexpectedly superior efficacy compared to citalopram (the racemate) in patients suffering from severe depression and having a MADRS score of at least 29.

For these reasons, the presently claimed invention is non-obvious over the cited prior art. Applicants, therefore, respectfully request that this rejection be withdrawn.

CONCLUSION

In view of these remarks and arguments, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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